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COPPER-MEDIATED PERFLUOROALKYLATION OF HALOGENOTHIOPHENES

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SUMMARY

The title reaction leads to the formation of 2- and 3-perfluoroalkyl thiophenes. A carbenoid mechanism is invoked to explain the presence of a rearrangement product.

INTRODUCTION

A research project directed toward the synthesis of polymeric materials prompted us to prepare some thiophenes specifically substituted at the C(3) position by a perfluoroalkyl group.

It is known that direct perfluoroalkylation of thiophene (with *n*-perfluorodecyl iodide) produces the 3-isomer as the minor compound, the main product being the 2-isomer (92%) [1] . Since the work of Mc Loughlin and Thrower [2] , the copper mediated coupling of perfluoroalkyl iodides or bromides with halogenated aromatic compounds [3,4] or nucleoside derivatives [5] has been intensively studied. Starting from 2-iodothiophene and 1,3-diiodohexafluoropropane, Mc Loughlin *et al.* [2] obtained 1,3-dithienylhexafluoropropane. We applied their procedure to the preparation of 2-and 3-perfluoroalkylated thiophenes.

RESULTS

By heating in an open glass vessel (or a stainless-steel bomb for CF_3I) a mixture of 3 (or 2)-halogenated thiophene (one equivalent), perfluoroalkyl iodide (one equivalent) and copper-bronze (about three equivalents) in *N,N*-dimethylformamide (DMF) at 120-130°C for about 20 hours, monosubstituted thiophenes were obtained as a mixture of their 3- and 2-perfluoroalkylated isomers.

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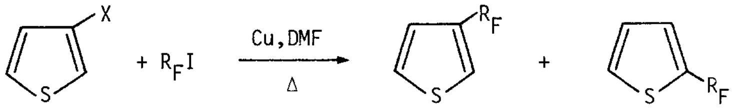


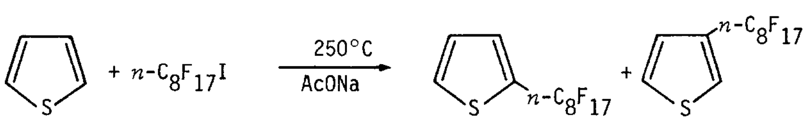
Major Minor

X=Br, I $R_F=CF_3, n\text{-}C_4F_9, n\text{-}C_8F_{17}$

When $R_F \neq CF_3$, the two isomers were found to be inseparable by standard separation procedures and the isomeric distribution was determined by ^{19}F NMR (Table 1). When $R_F=CF_3$ and X=Br no coupling product could be observed whereas with X=I, 3-(trifluoromethyl)thiophene was obtained along with unidentified lighter compounds. The existence of the 2-isomer could not be confirmed.

A survey of the literature [4] and our own experience [6] on halogenocyclohexenones indicates that the rearrangement we observed was not unusual in coupling experiments. Following Kobayashi's hypothesis [4], this might be due to the addition of the perfluoroalkyl anion to the C(2)-C(3) double bond, followed by a hydride ion shift. This may imply the formation of a transient carbenoid species (Scheme 1). Alternatively, direct attack of the R_F anion at the C(3) position may lead to the most favoured product, probably also by a concerted mechanism. The balance between the two orientations is clearly influenced by the nature of the halogen (X) on thiophene since the better the leaving group, the lower is the percentage of rearrangement. So, when one used *n*-perfluorooctyl iodide with 3-bromothiophene, 18 % of a rearranged product was obtained, but 3-iodothiophene yielded less than 4 % of the 2-perfluoro-*n*-octylthiophene. This type of rearrangement also took place to a small extent (<5 %) when one started from 2-bromothiophene (R_F=n-C_8F_{17}).

As 2-perfluoro-*n*-octylthiophene was obtained in poor yield (6 %) by copper coupling, we prepared it also, for the sake of comparison, by Knunyant's procedure for the perfluoroalkylation of benzenoid compounds [7]. Direct coupling between thiophene and the appropriate R_FI, at elevated temperature, in the presence of sodium acetate gave a mixture of the 2- and 3-isomers of perfluoro-*n*-octylthiophene (64 % yield from R_FI).



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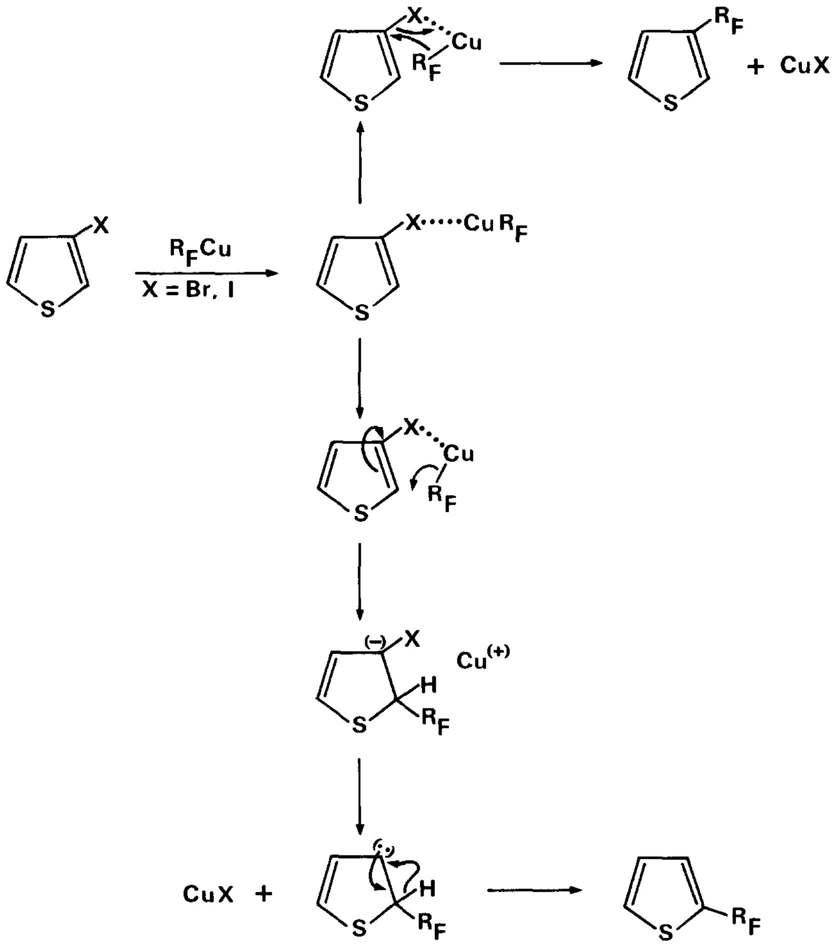


Scheme 1

Unambiguous identification of the various isomers was relatively easy by examination of their ^{19}F NMR spectra since a difluoromethylene group when directly bound to the ring shows a very different chemical shift from the other CF_2 groups. Furthermore, by ^{19}F NMR, fluorines of a C(2) bound CF_2 group have a smaller chemical shift, *i.e.* appear closer to the internal reference $CFCl_3$, than that of a C(3) bound CF_2 group. This was deduced from the study of 500 MHz ^1H NMR first order spectra of the fluorinated thiophenes which allowed an easy assignment of the structures (see Table 2), based on well-known values of coupling constants in various substituted thiophenes [8].

TABLE 1

Perfluoroalkylation of halogenothiophenes (ThX) with R_FI

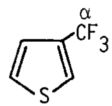
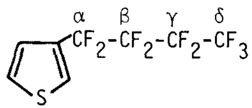
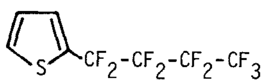
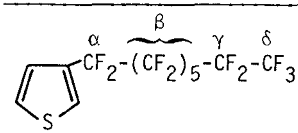
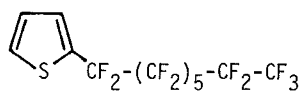
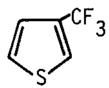
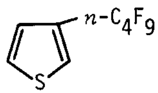
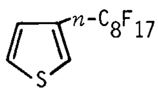
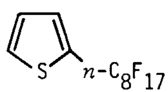
Compound	Starting ThX	Isolated yield (%/ThX)	Isomer Composition (%)	Bp °C (mmHg)	^{19}F NMR($CDCl_3$), Ø, ppm/$CFCl_3$, (structure, J(Hz)) α	β	γ	δ
	3-I	17	-	100	60.7 (t,1.1)			
	3-Br	30	82	72 (56)	107.7 (tm,12.7)	124.5 (m)	127.2 (m)	82.3 (tt,9.9,3.1)
			18		102.2 (tm)			
	3-I	50 (40,X=3-Br)	96 (82,X =3-Br)	95 (14)	108 (tm,12.5)	124 (m)	128.3 (m)	82.5 (tm,9.4)
			4 (18,X =3-Br)		102.5 (tm,12.5)			82.5 (tm,9.6)

TABLE 2

^{1}H-NMR (500 MHz) ($CDCl_3$). Chemical shifts (δ, ppm/TMS) and coupling constants (Hz) of perfluoroalkylated thiophenes

Compound	δ_2	δ_3	δ_4	δ_5	H-H Couplings	H-F Couplings[a]
	7.71	-	7.24	7.39	J_{24}=1.3 J_{25}=3.0 J_{45}=5.1	J_{2F}=1.1 J_{4F}=0.0 J_{5F}=1.1
	7.71	-	7.22	7.42	J_{24}=1.1 J_{25}=3.1 J_{45}=5.2	J_{2F}=1.1 J_{4F}=1.1 J_{5F}=1.5
	7.71	-	7.22	7.41	J_{24}=1.1 J_{25}=3.1 J_{45}=5.2	J_{2F}=1.1 J_{4F}=1.1 J_{5F}=1.5
	-	7.44	7.13	7.57	J_{34}=3.7 J_{35}=1.2 J_{45}=5.0	J_{3F}=? J_{4F}=1.5 J_{5F}=0.0

[a] See text for a discussion of assignments.

Nevertheless, as in 3-(trifluoromethyl)thiophene, the coupling constant J_{4-F} is zero, and it remains ambiguous for 3-perfluoro-*n*-butyl and 3-perfluoro-*n*-octylthiophenes since the coupling constant value we determined between C(4)-<u>H</u> and fluorine is 1.1 Hz. It is possible that this coupling takes place between the proton on C(4) and fluorine on the C(β) of the chain, rather than that on C(α). All other observed H-F coupling constants can reasonably be considered as occuring between protons and C(α) fluorine atoms.

EXPERIMENTAL

^{1}H NMR (nuclear magnetic resonance) spectra were recorded at 500 MHz on a Brüker WM-500 spectrometer and the chemical shifts (on the δ scale) are reported in parts per million (ppm) from tetramethylsilane (TMS) as internal reference. ^{19}F NMR spectra were recorded at 56.4 MHz on a Varian EM 360 L spectrometer. Chemical shifts are reported in ppm from $CFCl_3$ as internal reference.

The copper-bronze used was the commercial copper powder (Koch-Light Laboratories Ltd, Colnbrook, Bucks., England). 3-Bromothiophene [9], 2-bromothiophene [10] and 3-iodothiophene [11] were prepared following described procedures.

<u>Typical copper-mediated coupling experiment. 3-Perfluoro-*n*-octylthiophene [12]</u>

To a well-stirred suspension of copper-bronze powder (10 g ; 0.16 mol) in dry *N,N*-dimethylformamide (60 ml) was added 3-iodothiophene (10.5 g ; 50 mmol) followed by perfluoro-*n*-octyl iodide (32.8 g ; 60 mmol) and the mixture was heated under an inert atmosphere for 16 to 20 h at 120 to 130°C. After cooling and filtration of the solids over Celite, the liquid phase was poured into chilled hydrochloric acid (crushed ice ~ 75 g ; concentrated acid 75 ml) and then decanted. The lower (organic) layer was collected and the aqueous layer extracted with *n*-hexane. The combined extracts were washed with an aqueous solution of sodium thiosulfate, then water and dried ($MgSO_4$). After rotary evaporation of the solvent, careful distillation of the residue in an efficient column afforded a mixture of 3- and 2-perfluoro-*n*-octylthiophene (13 g ; 26 mmol). Analysis : Found : C, 27.98 ; H, 0.87 ; S, 6.87 %. $C_{12}H_3F_{17}S$ requires C, 28.70 ; H, 0.60 ; S, 6.38 %.

3-(Trifluoromethyl)thiophene

A 125 ml stainless-steel autoclave was charged with dry *N,N*-dimethyl formamide (50 ml), copper-bronze powder (25 g ; 0.4 mol) and 3-iodothiophene (15 g ; 71 mmol). The autoclave was closed, cooled to about -70°C, then evacuated. Trifluoromethyl iodide was introduced (≈ 40 g, 0.2 mol). After warming-up, the autoclave was placed in a rocking-oven and heated to 130°C for about 24 h. After cooling and degassing, the mixture was filtered over Celite and the filtrate roughly distilled at atmospheric pressure until the head temperature reached about 120°C. The distillate was distilled once more in an efficient column and the fractions between 99.5 to 101.5°C collected containing mainly 3-(trifluoromethyl)thiophene contaminated by lighter impurities (1.7 g, 11.2 mmol). A second crop (0.8 g) was obtained by treating the residual DMF solution with chilled hydrochloric acid (*vide supra*) and extraction with *n*-pentane. After drying of the organic extracts over $MgSO_4$, distillation under atmospheric pressure afforded contaminated 3-(trifluoromethyl)thiophene.

Pure samples were obtained by preparative vapor phase chromatography (DEGS column, 70-80°). Bp 100°C (Siwoloboff's method). IR (CCl_4) 1138 (s), 1163 (s), 1216 (m), 1295 (s), 1405 (w), 1425 (m), 3120 (w) cm^{-1}. Analysis : Found : C, 39.26 ; H, 1.87 %. $C_5H_3F_3S$ requires C, 39.47 ; H, 1,98.

Direct perfluoroalkylation of thiophene. 2-Perfluoro-*n*-octylthiophene

A 125 ml stainless-steel autoclave charged with thiophene (25 g ; 0.3 mol), perfluoro-*n*-octyl iodide (27.3 g ; 50 mmol) and sodium acetate (12 g ; 0.165 mol) was heated with shaking at 250°C for 8 h. After cooling, the mixture was poured into water and extracted with diethyl ether. The combined extracts were washed with an aqueous solution of sodium thiosulfate, then with water and dried ($MgSO_4$). Distillation afforded 2-perfluoro-*n*-octylthiophene (16 g ; 32 mmol) contaminated by *c.a.* 10 % of 3-perfluoro-*n*-octylthiophene. Analysis : Found : C, 28.01 ; H, 1.06 ; S, 7.02 %. $C_{12}H_3F_{17}S$ requires C, 28.70 ; H, 0.60 ; S, 6.38 %.

CONCLUSION

This method of copper-mediated perfluoroalkylation of thiophene is useful to prepare 3-perfluoroalkylthiophenes albeit in low yields and as a mixture of isomers. Nevertheless, reaction conditions have not been optimized as we used, with an aim of rationalization, nearly equimolecular quantities of halogenothiophene and perfluoroalkyl iodides (excepted with trifluoromethyl iodide we used on excess). Moreover, it appears that the use of iodothiophenes allowed us to minimize isomerisation. This is of importance since the isomers are probably rather difficult to separate.

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12 3-Perfluoro-*n*-butylthiophene was obtained and purified by the same procedure except that the solvent was distilled off at atmospheric pressure. Analysis (mixture of isomers) : Found : C, 31.90 ; H, 1.39 ; F, 58.28 ; S, 10.20 %. $C_8H_3F_9S$ requires C, 31.80 ; H, 1.00 ; F, 56.59 ; S, 10.61 %.